AMENDMENT(S) TO THE SPECIFICATION

Please replace the paragraph at column 1, lines 9-15 of U.S. Patent 6,440,392, with the following rewritten paragraph:

1. Field of the Invention

The present invention relates to [an] intranasal pharmaceutical compositions comprising calcitonin as an active ingredient and specific concentrations of citric acid or a salt thereof as a stabilizer and absorption enhancer.

Please replace the paragraph at column 1, lines 24-47 of U.S. Patent 6,440,392, with the following rewritten paragraph:

Given their size and chemical composition, calcitonins were originally administered by subcutaneous or intramuscular injection. Other routes of administration were technically difficult because calcitonins were poorly absorbed through tissue and were readily degraded by bodily fluids. Despite these obstacles, a formulation (U.S. Patent 5,759,565) was developed that could be administered via the nasal route. The nasal formulation was designed to be stored in a multi-dose container that was stable for an extended period of time and resisted bacterial contamination. The preservative in the formulation, benzalkonium chloride, was found to enhance the absorption of salmon calcitonin. However, benzalkonium chloride was reported (P. Graf et al., Clin. Exp. Allergy 25:395-400; 1995) to aggravate [rhintis] <u>rhinitis</u> medicamentosa in healthy volunteers who were given a decongestant nasal spray containing the preservative. It also had an adverse effect on nasal mucosa (H. Hallen et al., Clin. Exp. Allergy 25:401-405; 1995). Berg et al. (Laryngoscope 104:1153-1158; 1994) disclose that respiratory mucosal tissue that was exposed *in vitro* underwent severe morphological alterations. Benzalkonium chloride also caused significant slowing of the mucocilary transport velocity in the *ex vivo* frog palate test (P.C. Braga et al., J. Pharm. Pharmacol. 44:938-940; 1992).

Please replace the paragraph at column 3, lines 15-20 of U.S. Patent 6,440,392, with the following rewritten paragraph:

The compositions of the invention should also possess an appropriate isotonicity and viscosity. Preferably they have an osmotic pressure of from about 260 to about 380 mOsm/liter. Desired viscosity for the nasal spray is preferably less than 0.98 cP. In one embodiment, the osmotic pressure is from 250 to 350 mOsm/liter.

Please replace the paragraph at column 4, lines 44-50 of U.S. Patent 6,440,392, with the following rewritten paragraph:

In single-dose studies, blood samples are collected prior to dosing and at 5, 15, 30, 60 and 120 minutes after dosing. In multiple-dose studies, blood samples are collected prior to dosing and at 30, 60, 90, 120 and 150 minutes after the administration of the first dose. Blood samples are always collected immediately before the administration of any additional [costs] doses.

Please replace the paragraph at column 5, lines 7-22 of U.S. Patent 6,440,392, with the following rewritten paragraph:

EXAMPLE 1

The following study examines the effect of the concentration of citric acid on the bioavailability and plasma concentration of nasally administered salmon calcitonin. Rats were administered intranasally as described previously [20 µl] 20 µg of rsCT (200 µg/ml) in 0.85% sodium chloride, 0.1% TWEEN® 80, 0.2% phenylethyl alcohol, 0.5% benzyl alcohol and varying amounts of citric acid adjusted to pH 3.7 at t=0, [20] 30, 60 and 90 minutes. Samples of blood were taken prior to the administration of rsCT at these time points as well as at t=120 and 150 minutes. The resulting plasma samples were analyzed for rsCT by radioimmunoassay. Maximum rsCT levels were usually detected at t=120 minutes. The results of this study as shown in Table 1 indicate that

the bioavailability and peak concentration of rsCT was a function of the concentration of citric acid in the formulation.

Please replace TABLE 1 at column 5 at lines 24-35 with the following new TABLE 1:

TABLE 1

EFFECT OF THE CONCENTRATION OF CITRIC ACID ON THE BIOAVAILABILITY AND PLASMA CONCENTRATION OF SALMON CALCITONIN ADMINISTERED INTRANASALLY TO RATS

Citric acid (pH 3.7) mM	Bioavailability (percent ± sdev)	Maximum plasma sCT (ng/ml ± sdev)
0	[0.89 ± 0.19] 1.31 ± 0.77	[1.10 ± 0.52] 1.42 ± 0.78
10	[3.14 ± 1.77] 3.57 ± 1.39	[3.66 ± 1.67] 3.58 ± 1.42
25	[5.01 ± 2.34] 6.49 ± 2.93	[5.11 ± 2.09] 5.98 ± 2.30
50	[6.15 ± 1.31] 6.16 ± 1.31	6.05 ± 1.30
100	13.36 ± 3.38	[12.98 ± 3.96] 12.98 ± 3.93

Please replace the paragraph at column 5, lines 38-49 of U.S. Patent 6,440,392, with the following rewritten paragraph:

EXAMPLE 2

The following study examines the effect of different preservatives on the plasma concentration of nasally administered salmon calcitonin. Rats were administered intranasally as described previously [20 µl] 20 µg of sCT (200 µg/ml) in 0.85% sodium chloride, 0.1% TWEEN® 80 and a combination preservatives of either 0.2% phenylethyl alcohol and 0.5% benzyl alcohol or 0.27% methyl parabens and 0.04% propyl parabens at t=0, 30, 60 and 90 minutes. The results of this study as shown in Table 2 indicate that the bioavailability and peak concentration of rsCT are not significantly affected by the addition of the different preservatives.

Please replace TABLE 2 at column 5 at lines 51-62 with the following new TABLE 2:

TABLE 2

EFFECT OF PRESERVATIVES ON THE AVAILABILITY AND PLASMA CONCENTRATION OF SCT ADMINISTERED INTRANASALLY TO RATS

Preservatives	Bioavailability (percent ± sdev)	Maximum plasma sCT (ng/ml ± sdev)
None	1.14 ± 0.87	1.24 ± 0.79
0.2% phenylethyl alcohol - 0.5% benzyl alcohol	[0.89 ± 0.19] 1.31 ± 0.77	[1.10 ± 0.52] 1.42 ± 0.78
0.27% methyl parabens - 0.04% propyl parabens	1.08 ± 0.86	1.47 ± 1.46

Please replace the paragraph at column 5, lines 65-67 and (carryover paragraph) at column 6, lines 1-15 of U.S. Patent 6,440,392, with the following rewritten paragraph:

EXAMPLE 3

The following study examines the effect of the concentration of citric acid on the stability of salmon calcitonin stored for varying periods at a temperature of 50°C. Nasal formulations containing sCT (200 μg/ml) in 0.85% sodium chloride, [0.25%] 0.2% phenylethyl alcohol, 0.5% benzyl alcohol and 0.1% TWEEN® 80 were adjusted to [pH 3.7] pH 3.8 with either HCl or the indicated amount of buffered citric acid. The formulations were stored at 50°C in sealed glass containers for the indicated amount of time and analyzed for sCT by high performance liquid chromatography. The results as shown in Table 3 indicate that in the absence of citric acid, the amount sCT in the formulation decreased steadily between 0 and 9 days after the study was begun. In the presence of citric acid (10-50 mM) the rate of disappearance of sCT decreased significantly. However, as the concentration of citric acid was further increased, the rate of sCT disappearance

from vials stored at 50°C increased in proportion to the amount of buffered citric acid in the formulation.

Please replace TABLE 3 at column 6, lines 17-33 with the following new TABLE 3:

TABLE 3

EFFECT OF THE CONCENTRATION OF
CITRIC ACID ON THE STABILITY OF
sCT STORED FOR VARYING PERIODS AT 50°C

Percent sCT Recovered					
Citric Acid (pH [3.7] 3.8)	0 mM	10 mM	[20] 25 mM	50 mM	100 mM
Days at 50°C					
0	100	100	100	100	100
3	83	94	91	90	87
6	53	90	87	83	77
9	24	82	78	73	66
15	22	74	68	61	[20] 52